REMARKS

Status of the Claims

Claims 1 and 3-12 are currently pending in this application. In this amendment, claims 1 and 3 have been amended to incorporate the limitation of claim 4, and claim 5 has been amended to correct claim dependency. Claims 4 and 12 have been canceled without prejudice or disclaimer. No new matter has been added by way of this amendment. Upon entry of the amendment, claims 1, 3 and 5-11 will be pending. Entry of the amendment and reconsideration on the merits are respectfully requested.

Rejection under 35 U.S.C. § 112

Claim 12 stands rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim allegedly contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Without acquiescing to the Office's reasoning, claim 12 has been canceled without prejudice or disclaimer, solely to advance the prosecution of this application, thereby rendering this ground for rejection moot.

Rejections under 35 U.S.C. § 102

Applicants appreciate the Office's withdrawal of the earlier rejection of claim 1 under 35 U.S.C. § 102(b) in view of the amendments to the claim.

Rejections under 35 U.S.C. § 103

Nakao in View of Karp and Kuffner

Claims 1, 3-5 and 7-10 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nakao *et al.* (*Genome Informatics* 1999, 10:94-103, hereinafter "Nakao") as supported by the KEGG table of contents as of February 1999 (hereinafter "KEGG", *available at*: http://web.archive.org/web/19990203053246/www.genome.ad.jp/kegg/kegg2.html), in view of Karp *et al.* (*Trends in Biotech.* 1999, 17:275-281, hereinafter "Karp") and Kuffner *et al.* (*Bioinformatics*, 2000, 16(9): 825-836, hereinafter "Kuffner").

The Office alleged that Nakao discloses a method of metabolism reconstruction for both normal and disease states, wherein data regarding a eukaryotic organism's metabolism is collected, the data are linked to metabolic pathways, and interconnections are identified to create a map of the organism's metabolism. The Office acknowledged that Nakao does not teach identification of drug targets, as recited in the instant claims 3-11. To cure this deficiency of Nakao, the Office cited Karp, which allegedly teaches that new drug targets may be identified through the analysis of pathway genome databases and that that integrated genome-metabolic pathways provide a framework for improved drug discovery. The Office further cited Kuffner, which allegedly teaches a method for combining the information found in various metabolic databases to produce a differential metabolic display (DMD), which allows the comparison between disease pathways and non-disease pathways. The Office asserted that it would have been obvious to one of skill in the art to modify the method of reconstructing an organism's metabolism of Nakao with the drug target identification of Karp because Karp teaches that that integrated genome-metabolic pathways provide a framework for improved drug discovery. The Office further asserted that it would have been obvious to modify the method of reconstructing metabolism with collected data of Nakao and the use of pathways to identify targets of Karp with the DMDs of Kuffner because Kuffner teaches that DMDs allow the display of significant differences in order to identify gaps in specific pathways and enable the interpretation of expression data by making predictions for proteins of unknown function and to propose the existence and/or absence of specific proteins or protein functions.

Nakao in View of Karp and Kuffner and Further in View of Okubo

Claims 1, 3 and 6 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nakao as supported by KEGG, in view of Karp and Kuffner as applied to claims 1 and 3-5 above, and further in view of Okubo *et al.* (*Nature Genetics* 1992, 2:173-179, hereinafter "Okubo").

The Office acknowledged that Nakao in view of Karp and Kuffner as applied to claims 1 and 3-5 above does not teach the use of EST data, as recited in the instant claim 6. To cure this deficiency of Nakao, Karp and Kuffner, the Office cited Okubo, which allegedly teaches the use of EST data for gene mapping. The Office asserted that it would have been obvious to one of skill in the art to modify the method of metabolism reconstruction of Nakao in view of Karp and Kuffner as applied to claims 1 and 3-5 above by incorporating the EST data of Okubo because Okubo teaches that a map of expressed genes will facilitate the search for biologically and industrially interesting genes.

Nakao in View of Karp and Kuffner and Further in View of Kumar and Tile D4

Claims 1, 3 and 11 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Nakao as supported by KEGG, in view of Karp and Kuffner as applied to claims 1 and 3-5 above, and further in view of Kumar (*React. Funct. Polymers*, 2000, 46: 1-27, hereinafter "Kumar") and Tile D4 of the Boerhinger Biochemical Pathways Map (Roche Applied Science, 1993 *available at*: http://www.expasy.org/cgi-bin/show_image?D4&up, hereinafter "Tile D4").

The Office acknowledged that Nakao in view of Karp and Kuffner as applied to claims 1 and 3-5 above does not teach a pathway comprising a chitinase, as recited in the instant claim 11. To cure this deficiency of Nakao, Karp and Kuffner, the Office cited Tile D4, which allegedly shows a biochemical pathway comprising a chitinase, and Kumar, which allegedly teaches that chitin is a functional material of high potential. The Office asserted that it would have been obvious to one of skill in the art to modify the method of metabolism reconstruction of Nakao in view of Karp and Kuffner as applied to claims 1 and 3-5 above with a pathway comprising a chitinase as

shown in Tile D4 because Kumar shows the wide range of beneficial applications of chitin and because the substitution of a metabolic pathway reconstructed to comprise a chitinase for another pathway would have yielded predictable results.

Applicants respectfully traverse all these rejections for the reasons set forth below.

The obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)). To establish a *prima facie* case of obviousness a three-prong test must be met. First, the prior art reference must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). Second, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference to achieve the claimed invention. *KSR* at 1731. And third, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Rejections on obviousness grounds cannot be sustained by mere conclusory statements. *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2007) (citations omitted). Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Evidence of an unobvious or unexpected advantageous property can rebut prima facie obviousness. MPEP § 716.02(a).

As an initial matter, claims 1 and 3 have been amended to recite "mammalian organism" instead of "eukaryotic organism". The amendment has ample support in the specification as filed and better reflects the main focus of the present invention, which is pathway reconstruction of complex metabolic and signaling pathways and drug target identification for complex organisms (e.g., humans).

As Applicants explained in the Response filed on May 19, 2008, the present invention is based on three building blocks: (1) metabolic reactions and their interconnections forming metabolic pathways/networks; (2) molecular data (genes and proteins); and (3) links between the genes and proteins participating in the metabolic pathways and related diseases or disorders as annotated from the literature. As explained in the present specification at page 8, paragraph 2, "One feature of the reconstruction is the incorporation of human diseases. By activating a link to diseases, a user can see lists of diseases associated with the pathway. From these lists, pages for individual diseases can also be accessed. These pages contain lists of enzymes, reactions, and pathways that have been linked to a disease. In addition, one can view notes describing various aspects of a disease mechanism, its metabolic causes, and/or its manifestations." The ultimate result is a "disease network," comprising metabolic pathways, reactions, compounds and enzymes related to a particular disease (specification at page 6, paragraph 2). Using such a "disease network", it is possible to identify diseases related by common metabolic pathways, reactions, compounds or enzymes, which is a valuable tool for predicting and overcoming adverse drug-drug interactions.

Applicants respectfully submit that the Office has mischaracterized the teachings of Nakao, conflating two completely different components of the KEGG system. Nakao teaches that "[o]ne of the main features of KEGG is a collection of pathway maps, which computerizes the network information of molecular interactions such as for metabolism and signal transduction [KEGG/PATHWAY]" (page 94). Nakao further teaches that "[a]nother feature of KEGG is a collection of genome maps for completely sequenced organisms, as well as for the fruit fly, mouse, and human [KEGG/GENOME]" (*id.*). The KEGG Table of Contents cited by the Office reflects these two components. The top two tables refer to the pathway maps and molecular catalogs, which are not species-specific, i.e., information for different enzymes, metabolic pathways and regulatory pathways is pooled from a number of different species (page 1). The bottom tables refer to genome maps and gene catalogs, which include, *inter alia*, collections of human and mouse genes (page 2). Thus, while Nakao may teach integrating its species-specific genome database with its non-species specific metabolic pathway database, it does not teach or suggest pathway reconstruction of a single mammalian organism and integrating the resulting pathways with gene expression and other data from the same mammalian organism. Neither does Nakao teach or suggest incorporating functional

and/or high-throughput screening information. As Applicants pointed out in the previous Response, Nakao teaches primarily reconstruction of microbial metabolic pathways (*e.g.*, *Saccharomyces cerevisiae* and *Synechocystis*, see pages 99-101). The fact that the KEGG/GENOME database contained collections of mammalian genes does not change this conclusion for the simple reason that the KEGG/PATHWAY database did not contain mammalian-specific metabolic pathways.

Karp teaches that integrated pathway-genome databases, in conjunction with visualization and analysis software, provide a framework for improved understanding of microbial physiology and for antimicrobial drug discovery (*see* abstract). Similarly, the PETRI nets of Kuffner were known to be applicable only for modeling small biological systems (*see* page 826, left column). Consistent with that notion, the specific examples disclosed in Kuffner only involve relatively simple organisms, such as, for example, *Saccharomyces cerevisiae* (yeast) and *Mycoplasma genitalium* (*see, e.g.*, pages 829 and 834). Notably, neither Karp nor Kuffner contains a single reference to mammalian or human pathways. Moreover, even though Kuffner does make broad references to disease states, it is not clear what disease states it is referring to in view of the fact that the PETRI nets are only capable of modeling small biological systems. As such, it is respectfully submitted that Kuffner does not constitute an enabling reference for the purposes of obviousness analysis. The teachings of Okubo, Kumar and Tile D4 relate to limitations of dependent claims 6 and 11 and therefore do not cure the fatal deficiencies of Nakao in view of Karp and Kuffner.

As pointed out previously, the main focus of the presently claimed approach is on mammalian metabolic pathways – proteins that may be affected by drugs in order to alleviate a disease. The main idea of the present invention is that combining the data about what genes/proteins have been linked to a particular disease in multiple independent studies with information on their roles and positions in mammalian metabolic pathways allows reconstructing different versions of pathways (one for health and one for each disease of interest). That, in turn, helps to make a more informed decision regarding drug target identification and selection even in the absence of relevant disease-specific genomics or proteomics data. Disease-specific genomics or proteomics data may be used to further refine target selection.

In light of the foregoing, it is apparent that none of the combinations of the cited prior art references teaches each and every element of the claimed invention as amended. Both the disclosed software tools and the scientific information available at the time these documents were published were insufficient to enable the presently claimed methods. Accordingly, Applicants respectfully submit that the Office has failed to establish *prima facie* obviousness, and therefore this rejection under 35 U.S.C. § 103(a) may properly be withdrawn.

The rejection is rebutted by secondary indicia of nonobviousness

Applicants further aver that by submission of evidence of secondary indicia of nonobviousness they can overcome an obviousness rejection, even if, *arguendo*, the Office has showed sufficient evidence of *prima facie* obviousness.

The secondary considerations are essential components of the obviousness determination. *See In re Emert*, 124 F.3d 1458, 1462, 44 USPQ2d 1149, 1153 (Fed. Cir. 1997). This objective evidence of nonobviousness includes copying, long felt but unsolved need, failure of others, *see Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), commercial success, *see In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689-90 (Fed. Cir. 1996), unexpected results created by the claimed invention, unexpected properties of the claimed invention, *see In re Mayne*, 104 F.3d 1339, 1342, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997); *In re Woodruff*, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990), licenses showing industry respect for the invention, *see Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 957, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 316, 227 USPQ 766, 771 (Fed. Cir. 1985), and skepticism of skilled artisans before the invention, *see In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988).

Applicants submit herein sufficient evidence of secondary indicia of nonobviousness to rebut any possible *prima facie* case. By submission of a declaration under 37 C.F.R. §132 of Dr. Andrej Bugrim, Chief Operating Officer for GeneGo, Inc., Applicants provide objective evidence of nonobviousness that the instant claimed invention has fulfilled a long-felt need in the industry and has achieved unprecedented commercial and scientific success as evidenced by licensing and praise

of GeneGo's flagship product, MetaCore™, and other related systems biology software products. As explained in detail in the declaration and summarized below, MetaCore™ is directly based on the methods of the presently claimed invention, and therefore its commercial and scientific success is believed to be the direct result of the presently claimed invention. Accordingly, Applicants respectfully submit that this objective evidence of nonobviousness is sufficient to rebut a possible *prima facie* case of obviousness.

In his declaration, Dr. Bugrim declares that beginning in the early 1990s, the biomedical community sensed a growing need for integrating information on metabolic and other pathways and reconstructing biological processes in health and disease. Some of the most notable public projects in this area include the Kyoto Encyclopedia of Genes and Genomes (KEGG, cited in the OA), the Enzymes and Metabolic Pathways (EMP), the Biomolecular Interaction Network Database (BIND), BioCarta and EcoCyc. According to press releases issued at that time, tens of millions of dollars were invested in each of these projects. Even though these projects resulted in free, public-domain pathway analysis resources, they were unable to fully satisfy the needs of the scientific community in terms of reconstructing comprehensive organism- and condition-specific pathways and providing adequate tools for functional analysis of high-throughput molecular profiles. Some of the principal shortcomings of these public resources are:

(a) Lack of organism specificity, *i.e.*, data points from different organisms were pooled together, resulting in inconsistent and often incorrect pathways;

(b) Lack of comprehensive coverage, *i.e.*, most resources covered limited areas of cellular functionality but failed incorporate the full spectrum of biological processes;

(c) Inability to integrate heterogeneous information on metabolism and cell signaling with clinical and other phenotypical data; and

(d) Inability to combine pathways with high-throughput molecular data (*e.g.*, gene expression, proteomics, metabolomics).

Dr. Bugrim further declares that there have been multiple attempts by GeneGo's competitors to develop commercial tools that would allow analysis of high-throughput molecular data in the context of biological pathways and reconstruction of disease pathways. The list of private

companies that have attempted to develop such software includes Informax, Inc. (acquired by Invitrogen Corp.; now part of Life Technologies Corp.), OmniViz, Inc. (acquired by BioWisdom Ltd.), Lion Bioscience Ltd. (acquired by BioWisdom Ltd.), Genedata AG and several others. None of these attempts have resulted in commercially successful products, and many of these companies have ceased to exist as independent entities.

Dr. Bugrim further declares that when GeneGo, Inc. applied for federal Small Business Innovation Research (SBIR) and Advanced Technology Program (ATP) funding in 2002 in order to create a commercial embodiment of the presently claimed invention, a number of expert reviewers expressed reservations that the project would not be feasible in view of the failed prior attempts by other companies and academic institutes.

Dr. Bugrim further declares that GeneGo, Inc. has successfully developed and marketed its flagship product, the MetaCore™ pathway analysis software, based on the presently claimed invention. Subsequently, additional products and services were developed and marketed that also utilize elements of the claimed invention. MetaCore™ was first marketed in 2004 and has so far generated approximately $14,000,000 in sales. MetaCore™ is now licensed to over 200 institutional customers with thousands of individual users. The list of customers includes virtually every major pharmaceutical company, many mid-size and small biotech firms, over 50 major research universities and a number of U.S. Government agencies such as the National Institutes of Health (NIH), the Department of Defense (DOD), the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA). At the present time, approximately 50% of MetaCore™ customers are located in the U.S., 40% in Europe and 10% in Asia. Additionally, a number of "GeneGo Centers of Excellence" have been established at major universities, where use of MetaCore™ is now incorporated into the curriculum.

Dr. Bugrim further declares that despite the availability of the above-mentioned public-domain resources free of charge starting in the mid-1990s, GeneGo, Inc. has been able to license its MetaCore™ product to hundreds of customers at rates ranging from $3000/year for an individual

academic user to $500,000/year for a full commercial institutional license. Moreover, MetaCore™ has enjoyed annual sales growth rates of 40-60% since its release in 2004.

Dr. Bugrim further declares that MetaCore™ has received abundant praise from GeneGo, Inc.'s customers, partners and collaborators. A small sample of testimonials is reproduced below. A much longer list of testimonials may be found online at http://www.genego.com/testimonials.php.

> "We chose MetaCore™ as it has the most comprehensive, detailed database of human metabolism and signaling, and is also a one-stop shop for our systems analysis needs. Experimental data in nutrition are inherently complex, as the diet-influenced changes in disease onset and progression are subtle and multi-factorial. We also have the data from both human and model animals. In MetaCore™, we can upload and compare all these data on the same networks and pathways and then analyze the networks with a variety of tools." Dr. Ben van Ommen, Senior Research Fellow, Nutritional Systems Biology, TNO.
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> "We spent quite some time evaluating systems biology platforms and were impressed by the depth and breadth of the MetaCore™ knowledge base." "MetaCore™ has impressive coverage of signaling and metabolic pathways and in-depth disease and tissue-specific data that is invaluable for our research. In addition, MetaCore™ has a flexible and powerful front-end that allows our bench scientists to integrate multiple data streams and algorithms to fully mine our bone therapy data." Dr. Daniel Chagnovich, Director of Research Operations, Velcura Therapeutics, Inc.
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> "MetaCore™ has grown to become a key component in the research toolbox in the life sciences, particularly within the pharmaceutical industry, and we are pleased to have the opportunity to work with GeneGo," commented Dr. Jonathan Sheldon, Chief Scientific Officer, InforSense Ltd.
>
> "We see MetaCore™ as a further step into systems biology, a novel discipline which holds much promise for pharmaceutical research," said Dr. Friedrich Rippmann, Director of Bio- and Chemoinformatics at Merck KGaA.
>
> "We were very pleased to work with the team at GeneGo on the identification of cattle orthologs. My group feels that MetaCore™ is currently the premier product for data mining and pathway analysis." Harris Lewin, Director of the Institute for Genomic Biology, University of Illinois at Urbana-Champaign.
>
> "MetaCore™'s extensive information content allows us to perform detailed data analysis of high throughput assay results that is currently not possible with any other

tool. MetaCore™ has been adopted as a favorite tool by our users from day one." Burak Kutlu, Ph.D., Research Scientist, Institute for Systems Biology.

Finally, Dr. Bugrim declares that the success of MetaCore™ stems directly from the novel combination of elements recited in the presently claimed methods. Had this novel combination been obvious to a person skilled in the art at the time the invention was made, MetaCore™ would not have become the commercial and scientific success that it is.

Applicants respectfully submit that after considering all the evidence of secondary indicia of nonobviousness, this rejection under 35 U.S.C. § 103(a) can properly be withdrawn.

Provisional Double Patenting

Claims 1, 3, and 6-8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-9 of the commonly owned copending Application No. 10/174,762.

Claims 3, 7 and 8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4 of the commonly owned copending Application No. 11/499,437.

Applicants respectfully request that the Office hold these provisional obviousness-type double patenting rejections in abeyance until such time as any of the claims in question are allowed.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **docket No. 655202000300**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 21, 2008

Respectfully submitted,

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